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I, KAY WARD, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. PP 9997 for a patent by FUJISAWA PHARMACEUTICAL CO., LTD. filed on 27 April 1999.

WITNESS my hand this
Twenty-seventh day of April 2000

K Ward

KAY WARD
TEAM LEADER EXAMINATION
SUPPORT AND SALES

PRIORITY DOCUMENT
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Regulation 3.2

Fujisawa Pharmaceutical Co., Ltd.

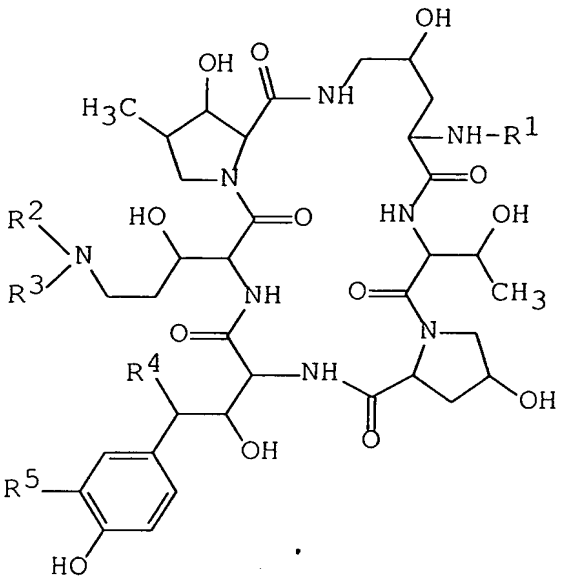
AUSTRALIA
Patents Act 1990

PROVISIONAL SPECIFICATION
for the invention entitled:

"New Compound"

The invention is described in the following statement:

general formula (I) :



(I)

wherein

R^1 is hydrogen or acyl group,

R^2 and R^3 are independently hydrogen, lower alkyl which may have one or more suitable substituent(s) or acyl group,

R^4 is hydrogen or hydroxy, and

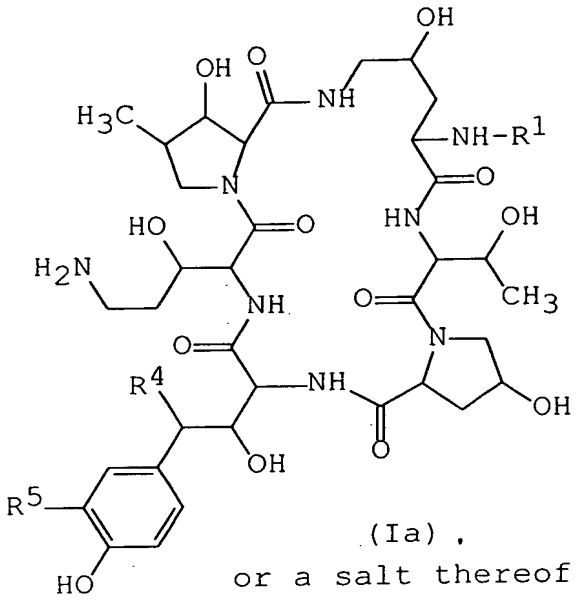
R^5 is hydroxy or hydroxysulfonyloxy,

or a salt thereof.

The new polypeptide compound (I) or a salt thereof can be prepared by the process as illustrated in the following reaction schemes.

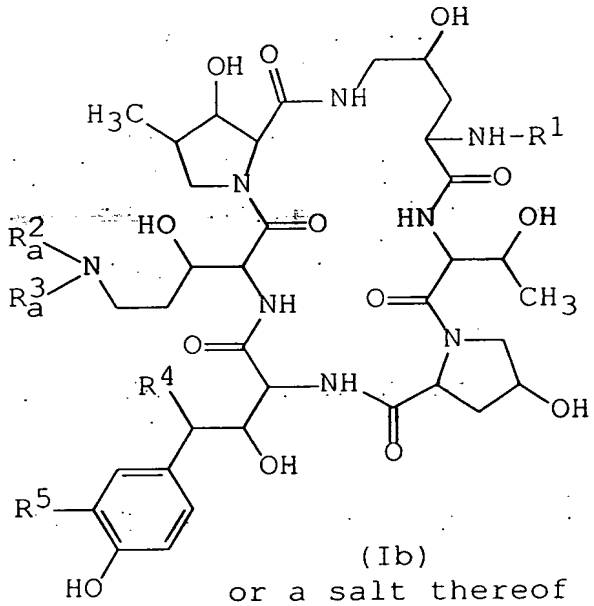
Process 1

Process 2



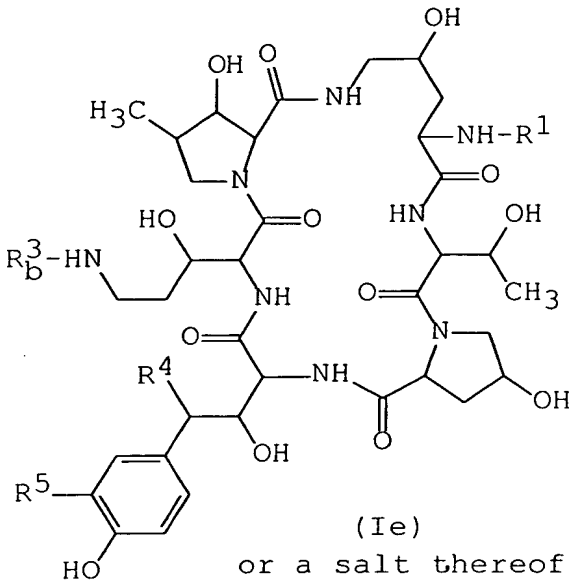
(Ia),
or a salt thereof

protective reaction



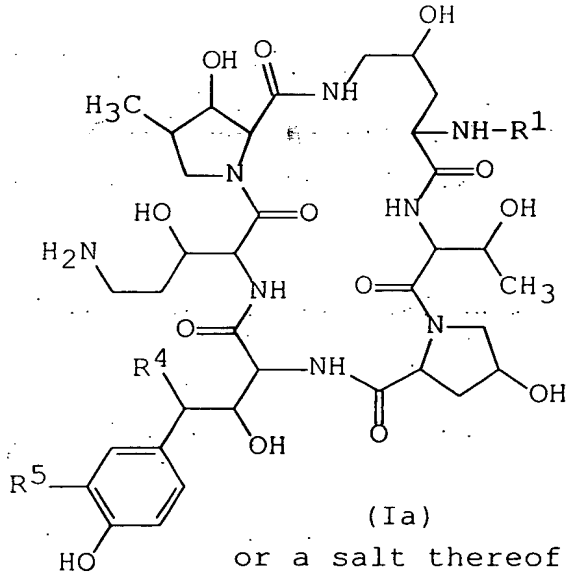
(Ib)
or a salt thereof

Process 4



(Ie)
or a salt thereof

elimination reaction



(Ia)
or a salt thereof

R_a^2 is hydrogen, lower alkyl which may have one or more suitable substituent(s) or acyl group,

R_a^3 is lower alkyl which may have one or more suitable substituent(s) or acyl group,

R_b^3 is amino protective group,

R_a^5 is hydroxysulfonyloxy, and

R_b^5 is hydroxy.

Suitable salt of the new polypeptide compound (I) is a pharmaceutically acceptable and conventional non-toxic salt, and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt;
a salt with an organic base, for example, an organic amine salt (e.g., triethylamine salt, diisopropylethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.);
an inorganic acid addition salt (e.g., hydrochloride hydrobromide, sulfate, phosphate, etc.);
an organic carboxylic sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.);
a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.).

Suitable examples and illustration of the various definitions in the above and subsequent descriptions of the present specification, which the present invention intends to include within the scope thereof, are explained in detail as follows :

The term "lower" is used to intend a group having 1 to 6

piperidyl, piperazinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, morpholino, etc.;

unsaturated condensed heterocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example thiazolidinyl, thiomorpholinyl, thiomorpholino, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 or 2 sulfur atom(s), for example, thienyl, dihydrodithiinyl, dihydrodithionyl, etc.;

unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, imidazothiadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-

heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.);
lower or higher alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl, heptyloxycarbonyl, etc.);
lower or higher alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.);
lower or higher alkoxysulfonyl (e.g., methoxysulfonyl, ethoxysulfonyl, etc.); or the like;

Aromatic acyl such as

aroyl (e.g., benzoyl, toluoyl, naphthoyl, etc.);
ar(lower)alkanoyl [e.g., phenyl(C_1-C_6)alkanoyl (e.g., phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutanoyl, phenylpentanoyl, phenylhexanoyl, etc.), naphthyl(C_1-C_6)alkanoyl (e.g., naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, etc.), etc.];
ar(lower)alkenoyl [e.g., phenyl(C_3-C_6)alkenoyl (e.g., phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentanoyl, phenylhexenoyl, etc.), naphthyl(C_3-C_6)alkenoyl (e.g., naphthylpropenoyl, naphthylbutenoyl, etc.), etc.];
ar(lower)alkoxycarbonyl [e.g., phenyl(C_1-C_6)alkoxycarbonyl (e.g., benzyloxycarbonyl, etc.), fluorenyl(C_1-C_6)alkoxycarbonyl (e.g., fluorenylmethyloxycarbonyl, etc.), etc.];
aryloxycarbonyl (e.g., phenoxycarbonyl, naphthyloxycarbonyl, etc.);
aryloxy(lower)alkanoyl (e.g., phenoxyacetyl, phenoxypropionyl, etc.);
arylcarbamoyl (e.g., phenylcarbamoyl, etc.);
arylthiocarbamoyl (e.g., phenylthiocarbamoyl, etc.);
arylglyoxyloyl (e.g., phenylglyoxyloyl, naphthylglyoxyloyl, etc.);
arylsulfonyl which may have 1 to 4 lower alkyl (e.g., phenylsulfonyl, p-tolylsulfonyl, etc.); or the like;

Heterocyclic acyl such as

heterocycliccarbonyl;

substituted with phenyl having (C_4-C_6)alkoxy, unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C_1-C_4)alkoxy(C_4-C_6)alkoxy, unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C_1-C_4)alkoxy(C_7-C_{14})alkoxy, saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having (C_1-C_4)alkoxy(C_7-C_{14})-alkoxy, unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having cyclo(C_4-C_6)alkyloxy, unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl saturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo(C_4-C_6)alkyl having cyclo-(C_4-C_6)alkyl, unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having phenyl substituted with (C_1-C_4)alkoxy(C_1-C_4)alkoxy, unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo(C_4-C_6)alkyl, unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) having cyclo(C_4-C_6)-alkyl, and the most preferred one may be imidazothiadiazolyl substituted with phenyl having pentyloxy, thiadiazolyl substituted with phenyl having methoxyhexyloxy, thiadiazolyl substituted with phenyl having methoxyoctyloxy, thiadiazolyl substituted with phenyl having methoxyheptyloxy,

imidazothiadiazolyl substituted with phenyl having piperazinyl substituted with cyclohexyl.

Suitable example of "lower alkyl" in the term of "lower alkyl which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkyl", in which the preferred one may be methyl, ethyl and propyl.

Suitable example of "suitable substituent(s)" in the term of "lower alkyl which may have one or more suitable substituent(s)" may be imino, amino, carbamoyl, lower alkoxy, and the like.

Suitable example of "lower alkyl which may have one or more suitable substituent(s)" may be iminomethyl, 1-iminoethyl, amidino, 1-imino-2-carbamoylethyl, 1-imino-3-methoxypropyl, carboxymethyl, 3-aminopropyl and 1-methylpyrazol-4-ylmethyl.

Suitable example of "acyl group" of R^2 and R^3 can be referred to aforementioned "acyl group", in which the preferred one may be acetyl, 2-acetyloxypropionyl, methylsulfonyl and 2,5-diaminopentanoyl.

Suitable example of "amino protective group" may be included in aforementioned "acyl group", a conventional protective group such as ar(lower)alkoxycarbonyl and lower alkoxycarbonyl, in which the preferred one may be phenyl-(C_1-C_4)alkoxycarbonyl and fluorenyl(C_1-C_4)alkoxycarbonyl and (C_1-C_4)alkoxycarbonyl, and the most preferred one may be benzyloxycarbonyl, fluorenylmethylcarbonyl and tert-butoxycarbonyl.

Process 1

The object compound (Ia) or a salt thereof can be prepared by reducing a compound (II) or a salt thereof.

Suitable salts of the compounds (Ia) and (II) may be the

reaction.

Process 2

The object compound (Ib) or a salt thereof can be prepared by subjecting the compound (Ia) or a salt thereof to protective reaction of amino.

This protective reaction may include acylation or alkylation reaction of amino, and can be carried out according to a conventional manner such as the one described in Examples or the similar manners thereto.

Process 3

The compound (Id) or a salt thereof can be prepared by subjecting the compound (Ic) or its reactive derivative at the sulfonic acid group or a salt thereof to hydrolysis reaction of the sulfonic acid group.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g., sodium potassium, etc.], an alkaline earth metal [e.g., magnesium, calcium, etc.], the hydroxide or carbonate or hydrogencarbonate thereof, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, or the like.

Suitable acid may include an organic acid [e.g., formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.], and an inorganic acid [e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.].

The elimination using Lewis acid such as trihaloacetic acid [e.g., trichloroacetic acid, trifluoroacetic acid, etc.], or the like preferably carried out in the presence of cation trapping agent [e.g., anisole, phenol, etc.].

The reaction is usually carried out in a conventional

water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium, sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc], iron catalysts [e.g. reduced iron, Raney iron, etc], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the

ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the mind of the compound (III) to be used.

Suitable salts of the compound (III) and its reactive derivative can be referred to the ones as exemplified for the object polypeptide compound (I).

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound (III) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide; N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine, ethoxyacetylene; 1-alkoxy-2-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride;

solvated compound [e.g., enclosure compound (e.g., hydrate, etc.)].

The object compound (I) or a salt thereof includes both its crystal form and non-crystal form.

It should be understood that the compounds in the present invention may include the prodrug form.

The patent applications and publications cited herein are incorporated by reference.

Biological property of the polypeptide compound (I) of the present invention

In order to show the usefulness of the polypeptide compound (I) of the present invention, the biological data of the representative compound is explained in the following.

Test (Antimicrobial activity) :

In vitro antimicrobial activity of the object compound of Example 5 disclosed later was determined by MIC_s in mouse serum method as described below.

Test Method :

The MIC_s in mouse serum were determined by the microdilution method using ICR mouse serum buffered with 20 mM HEPES buffer (pH 7.3) as a test medium. Inoculum suspension of 10^6 cells/ml were prepared by a hemocytometric procedure and diluted to obtain an inoculum size of approximately 1.0×10^3 cells/ml. Microplates were incubated at 37°C for 24 hours in 5% CO_2. The MIC_s were defined as the lowest concentrations at which no visible growth was observed.

Test Result : MIC (μg/ml)

Test compound / Test organism	The object compound of Example 5
Candida albicans FP-633	0.25

therapeutically effective amount of the object polypeptide compound (I) varies from and also depends upon the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.01-20 mg of the object polypeptide compound (I) per kg weight of human being in the case of intramuscular administration, a daily dose of 0.1-20 mg of the object polypeptide compound (I) per kg weight of human being, in case of oral administration, a daily dose of 0.5-50 mg of the object polypeptide compound (I) per kg weight of human being is generally given for treating or preventing infectious diseases.

Especially in case of the treatment of prevention of Pneumocystis carinii infection, the followings are to be noted.

For administration by inhalation, the compounds of the present invetion are conveniently delivered in the form of an aerosol spray presentation from pressurized as powders which may be formulated and the powder compositions may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery system for inhalation is a metered dose inhalation aerosol, which may be formulated as a suspension or solution of compound in suitable propellants such as fluorocarbons or hydrocarbons.

Because of desirability to directly treat lung and bronchi, aerosol administration is a preferred method of administration. Insufflation is also a desirable method, especially where infection may have spread to ears and other body cavities.

Alternatively, parenteral administration may be employed using drip intravenous administration.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

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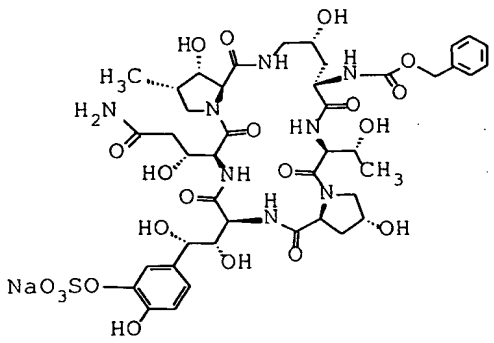
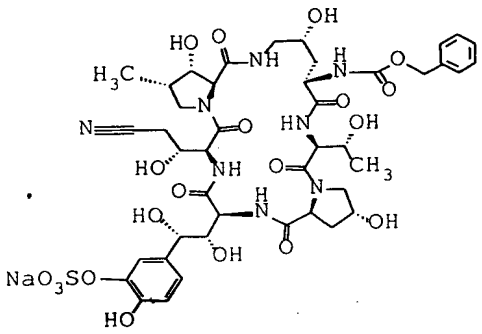
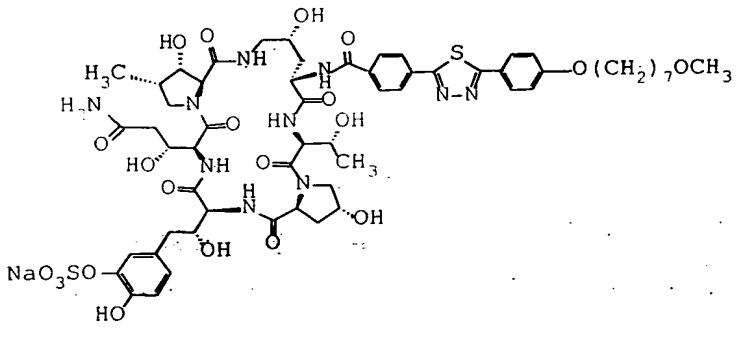
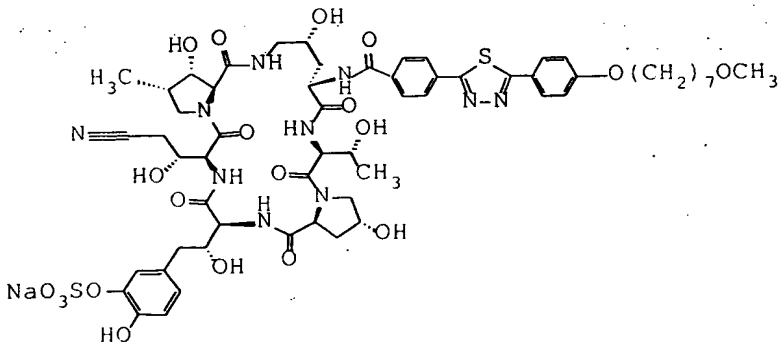
2	
	
3	
	

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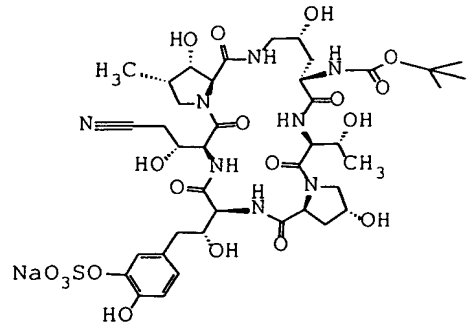
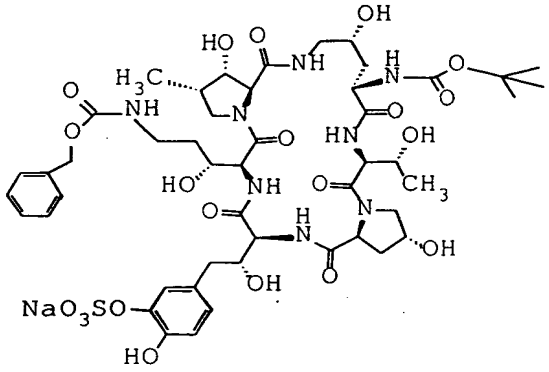
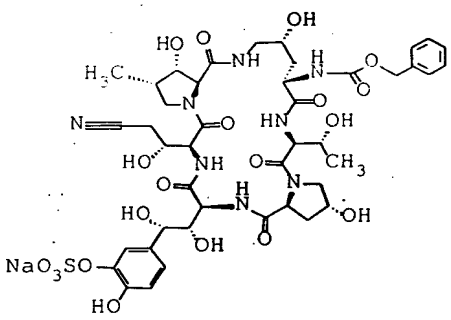
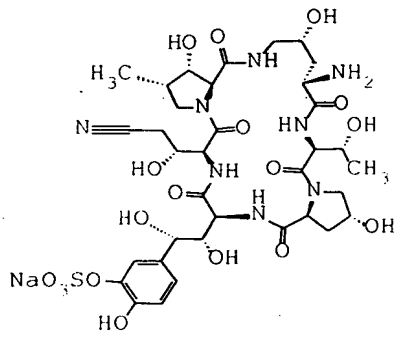
6	
	
7	
	

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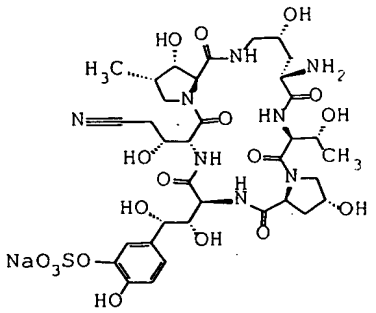
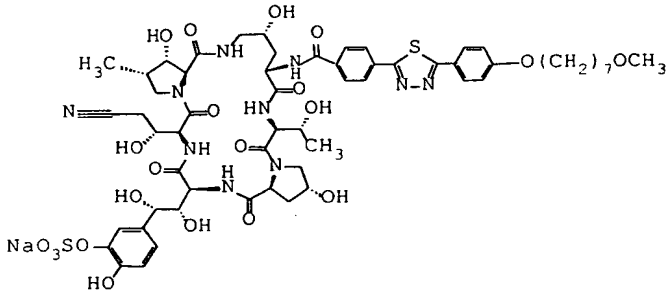
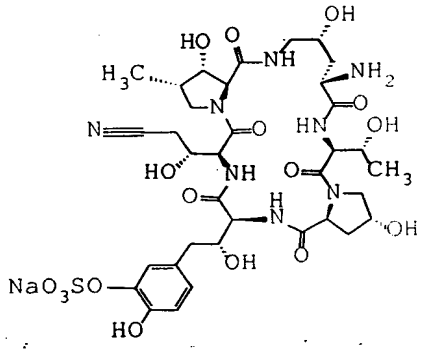
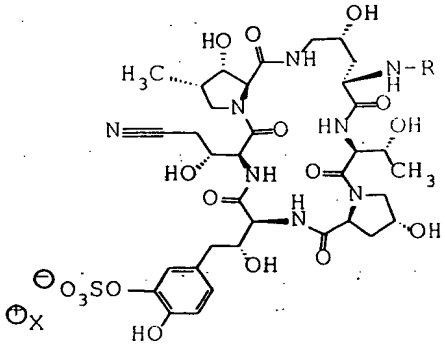
10	
	
11) 21	
	

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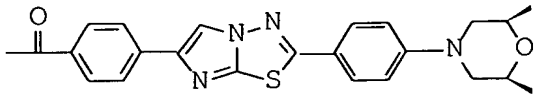
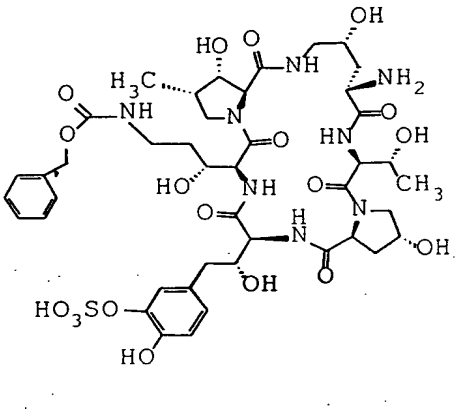
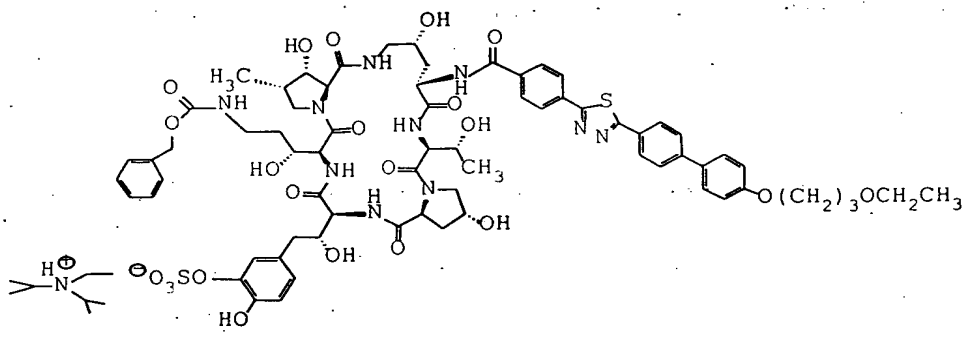
21		Na

Prepara-tion No.	Formula
22	
	

lyophilized to give Object compound (19.61 g) as an amorphous white powder.

NMR (DMSO-d_6, δ) : 0.95 (3H, d, J=6.8Hz), 1.07 (3H, d, J=5.5Hz), 1.34 (9H, s), 1.40-2.50 (9H, m), 2.80-3.0 (1H, m), 3.4-4.5 (15H, m), 4.70-5.40 (8H, m), 6.60-7.05 (6H, m), 7.25-8.00 (5H, m), 8.71 (1H, s)

MASS (m/z) : 1003.3 (M^+-H)

Preparation 2

A mixture of Starting compound (500 mg), N,N-dimethylformamide (5 ml) and synthetic A-4 zeolite (500 mg, Wako Chemical) was treated with diisopropyl ethylamine (66 mg), followed by methanesulfonyl chloride (58.5 mg) dropwise. After 1 hour at room temperature, further diisopropyl ethylamine (66 mg) and methanesulfonyl chloride (58.5 mg) were added. After 1.5 hours, additional diisopropylamine (66 mg) and methanesulfonyl chloride (58.5 mg) were added. After 1.5 hours, the mixture was filtered and the filtrate was poured into ethyl acetate. The precipitate was collected, washed with ethyl acetate and dried. The powder was dissolved in saturated sodium hydrogen carbonate solution then purified by ODS column chromatography (Daisogel SP-120 ODS Daiso) eluting with aqueous methanol (5-12.5%). Object compound-containing fractions were pooled, evaporated to remove methanol, and lyophilized to give Object compound (210 mg) as an amorphous white powder.

IR (KBr) : 2258.2, 1664.3, 1629.6, 1529.3, 1517.7, 1446.4, 1268.9 cm^{-1}

NMR (DMSO-d_6, δ) : 0.94 (3H, d, J=6.7Hz), 1.07 (3H, d, J=5Hz), 1.40-3.00 (9H, m), 3.10-4.50 (15H, m), 4.50-5.30 (10H, m), 5.66-5.69 (1H, m), 6.73 (1H, d, J=8.2Hz), 6.82 (1H, d, J=8Hz), 7.05 (1H, d, J=1.7Hz), 7.33 (5H, s), 7.20-7.50 (3H, m), 7.6-7.7 (1H, m), 8.27 (1H, d, J=8.3Hz), 8.84 (1H, s)

MASS (m/z) : 1081.3 ($M+Na^+$)

MASS (m/z) : 985.3 ($M-Na^+$)

Elemental Analysis Calcd. for $C_{40}H_{58}N_8O_{19}SNa \cdot 9H_2O$:

C 41.02, H 6.45, N 9.57

Found : C 41.35, H 6.42, N 9.61

Preparation 5

IR (KBr) : 2256.3, 1668.1, 1648.8, 1631.5, 1538.9, 1513.8, 1454.1, 1267.0 cm^{-1}

NMR (DMSO-d_6, δ) : 0.95 (3H, d, J=6.8Hz), 1.07 (3H, d, J=5.2Hz), 1.5-2.9 (10H, m), 3.2-4.5 (15H, m), 4.7-5.2 (9H, m), 5.7-5.8 (1H, m), 6.60-6.78 (2H, m), 6.96 (1H, br s), 7.33 (5H, s), 7.2-7.5 (3H, m), 7.7-7.8 (1H, m), 8.3 (1H, d, J=7.5Hz), 8.73 (1H, br s)

MASS (m/z) : 1065.2 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{43}H_{55}N_8O_{19}SNa \cdot 7H_2O$:

C 44.18, H 5.95, N 9.58

Found : C 44.21, H 5.82, N 9.54

Preparation 6

A solution of Starting compound (2.0 g) in methanol (100 ml) - water (20 ml) was treated with cobalt(II) chloride hexahydrate (1.89 g) and then stirred to give a pink solution. Sodium borohydride (1.5 g) was then added portionwise and then stirred for 1 hour at room temperature. The reaction mixture was filtered through a bed of celite, washing with methanol (100 ml) - water (30 ml) solution. The ice-cooled filtrate was then treated dropwise with a solution of benzyloxy carbonyl chloride (Z-chloride) (0.34 ml) in tetrahydrofuran (5 ml) and stirred for 1 hour at the same temperature. Ethyl acetate (50 ml) was added followed by water (200 ml) and after stirring ~ 5 minutes, the separated organic layer was discarded. The aqueous layer was adjusted to pH 8.8 and evaporated to remove organic solvent and then purified by ODS column chromatography, eluting with aqueous

C 40.70, H 5.95, N 10.85

Found : C 40.60, H 5.94, N 10.71

The following compound was obtained according to a similar manner to that of Preparation 7.

Preparation 8

IR (KBr) : 2256.3, 1648.8, 1631.5, 1538.9, 1513.8, 1267.0, 1083.8, 1047.2 cm^{-1}

NMR (DMSO-d_6, δ) : 0.96 (3H, d, J=6.7Hz), 1.08 (3H, d, J=5.9Hz), 1.7-2.1 (2H, m), 2.1-2.9 (7H, m), 3.1-4.6 (16H, m), 4.7-5.4 (6H, m), 6.1 (1H, br s), 6.70 (1H, d, J=8.2Hz), 6.75 (1H, d, J=8.2Hz), 6.96 (1H, br s), 7.2-7.55 (2H, m), 7.6-7.9 (2H, m)

MASS (m/z) : 885.3 ($M-Na^+$)

Elemental Analysis Calcd. for $C_{35}H_{49}N_8O_{17}SNa \cdot 6H_2O$:

C 41.34, H 6.05, N 11.02

Found : C 41.58, H 5.99, N 10.94

Preparation 9

A suspension of Starting compound (1.6 g) in dichloromethane (41 ml) was stirred with cooling at 5°C and treated with triethylsilane (1.1 ml), followed by trifluoroacetic acid (5.3 ml) dropwise over 30 minutes. After warming to room temperature, the clear solution was stirred for 2 hours, then poured into 450 ml of pH 6.86 phosphate buffer and adjusted to pH 8.5 with 4N-sodium hydroxide solution. Organic solvent was removed by evaporation and the remaining aqueous solution purified by ODS column chromatography, eluting with aqueous acetonitrile (5-20%). Object compound-containing fractions were pooled, evaporated, and lyophilized to give Object compound (1.25 g) as an amorphous white powder.

IR (KBr) : 1633.4, 1537.0, 1517.7, 1440.6, 1267.0 cm^{-1}

NMR (DMSO-d_6, δ) : 0.95 (3H, d, J=6.7Hz), 1.12 (3H, d,

Preparation 15

Preparation 16

Preparation 17

MASS (m/z) : 1237.3 ($M-Na^+$)

Preparation 18

A mixture of 4-[2-(4-pentyloxyphenyl)imidazo[2,1-b]-[1,3,4]thiadiazol-6-yl]benzoic acid (1.44 g), 1-hydroxybenzotriazole (714 mg), diisopropyl ethylamine (0.58 ml) and 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (810 mg) in N,N-dimethylformamide (50 ml) was stirred 6 hours at room temperature, then treated with Starting compound (2 g) and stirred overnight. Additional N,N-dimethylformamide (20 ml) was added and stirring continued for a further 5.5 hours. The clear solution was poured into ethyl acetate (1 l) and the precipitate collected and washed with isopropyl ether and dried to give crude Object compound (3.58 g), which was used directly in the next step.

The following compounds [Preparations 19 and 20] were obtained according to a similar manner to that of Preparation 18.

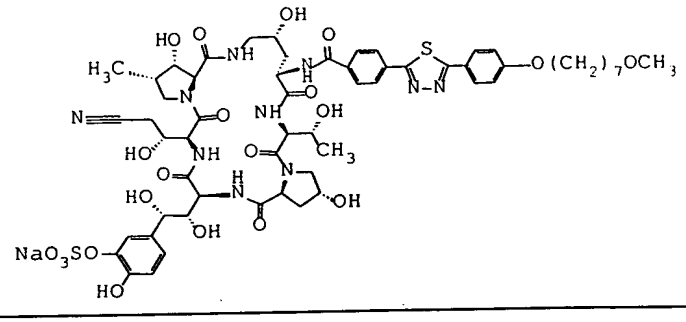
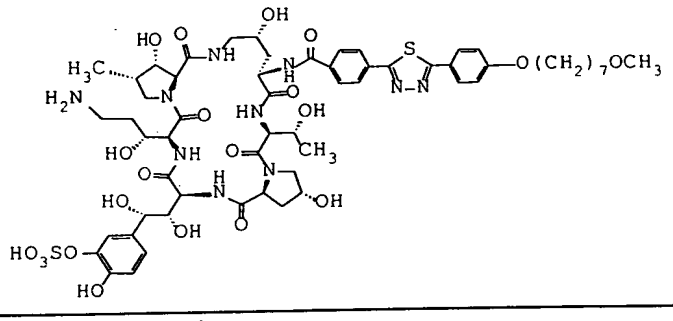
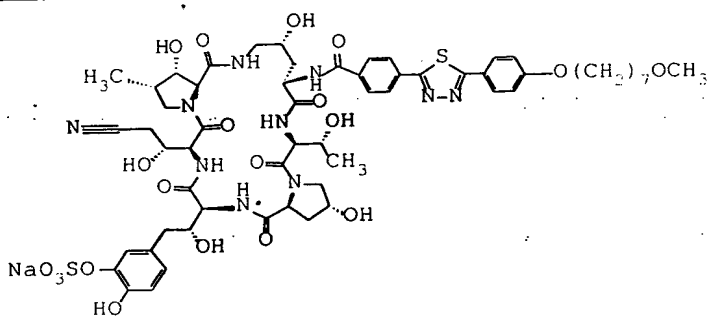
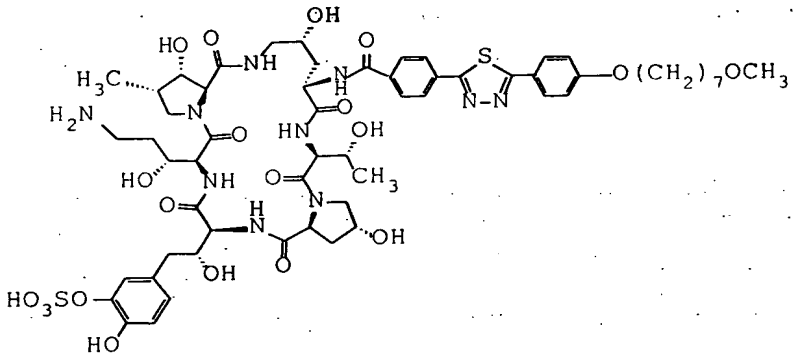
Preparation 19

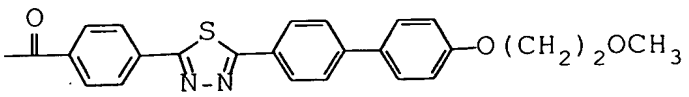
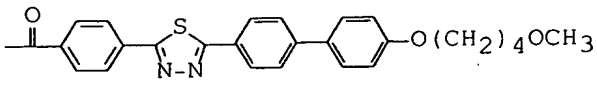
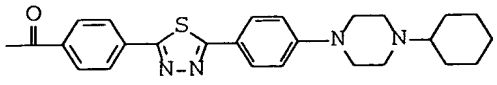
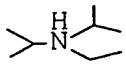
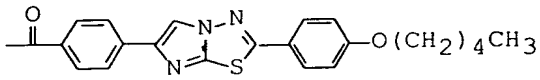
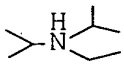
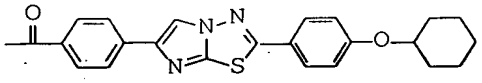
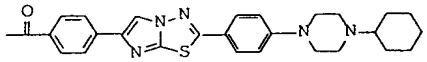
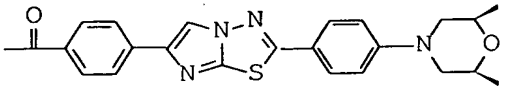
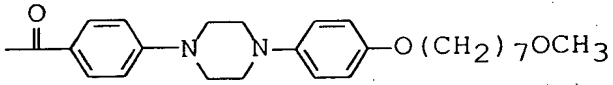
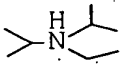
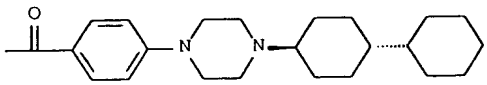
MASS (m/z) : 1286.3 ($M-Na^+$)

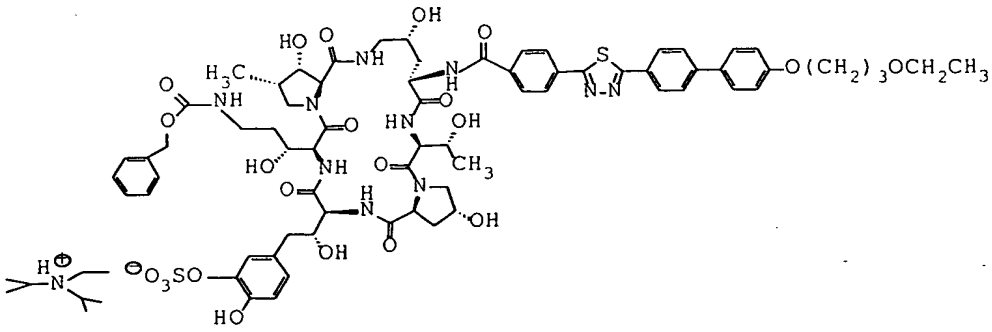
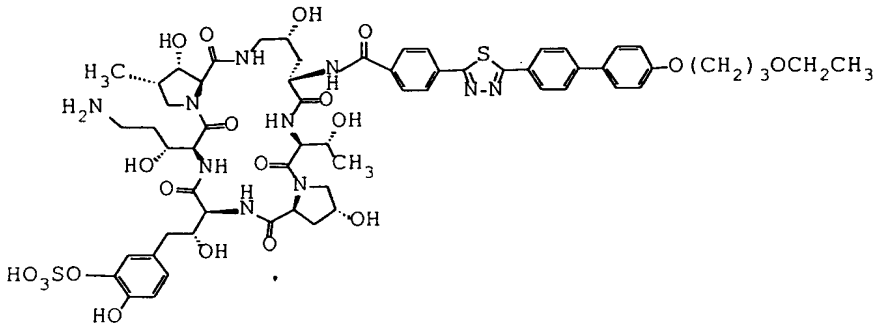
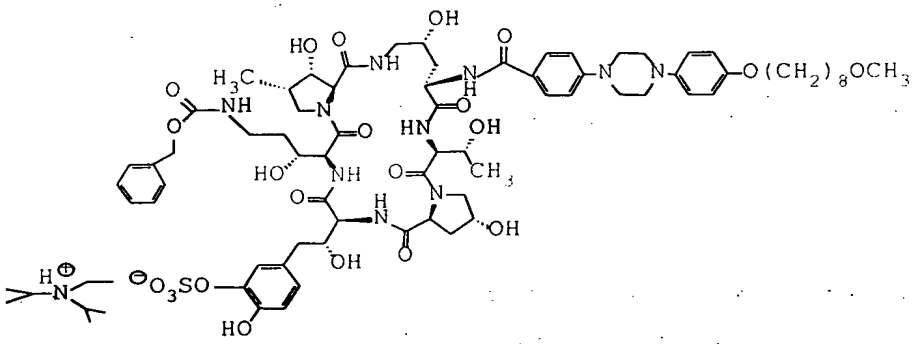
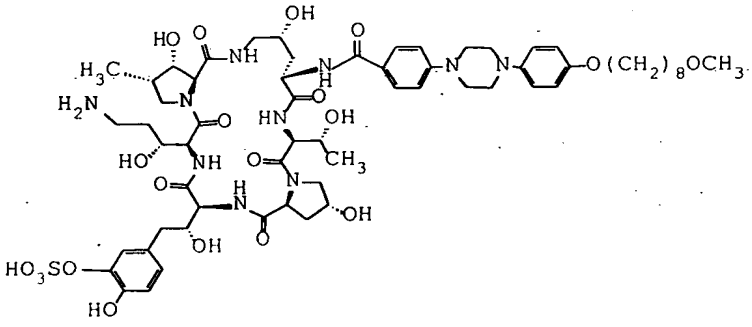
Preparation 20

MASS (m/z) : 1354.4 ($M-Na^+$)

The following compound was obtained according to a similar manner to that of Preparation 18.

Example No.	Formula
1	
	
2	
	

Example No.	R	X
5		Na
6		Na
7		
8		
9		Na
10		Na
11		Na
12		
13		Na

Example No.	Formula
16	
	
17	
	

IR (KBr) : 1648.8, 1631.5, 1538.9, 1515.8, 1442.5, 1257.4 cm^{-1}

NMR (DMSO-d_6, δ) : 0.98 (3H, d, J=6.7Hz), 1.24 (3H, d, J=5.6Hz), 1.40-1.60 (8H, m), 1.60-2.65 (15H, m), 2.80-5.50 (27H, m), 3.21 (3H, s), 3.30 (2H, t, J=6.3Hz), 6.72 (1H, d, J=8.1Hz), 6.78 (1H, dd, J=1.6 and 8.3Hz), 7.00 (1H, d, J=1.6Hz), 7.13 (2H, d, J=8.9Hz), 7.46 (1H, d, J=8.1Hz), 7.60-7.90 (2H, m), 7.97 (2H, d, J=8.7Hz),8.04-8.14 (4H, m), 8.24-8.27 (1H, m), 8.70-9.00 (2H, m)

MASS (m/z) : 1297.3 ($M-H^+$)

Elemental Analysis Calcd. for $C_{58}H_{78}N_{10}O_{20}S_2 \cdot 7.5H_2O$:
C 48.56, H 6.53, N 9.76

Found : C 48.56, H 6.31, N 9.63

Example 3

IR (KBr) : 1633.4, 1517.7, 1444.4, 1257.4 cm^{-1}

NMR (DMSO-d_6, δ) : 0.97 (3H, d, J=6.8Hz), 1.13 (3H, d, J=5.7Hz), 1.20-1.65 (10H, m), 1.65-2.65 (15H, m), 2.70-5.50 (27H, m), 3.21 (3H, s), 4.07 (2H, t, J=6.5Hz), 6.71 (1H, d, J=8Hz), 6.75-6.80 (1H, m), 6.98 (1H, d, J=1.6Hz), 7.13 (2H, d, J=8.9Hz), 7.46 (1H, d, J=8Hz), 7.55-7.85 (2H, m), 7.97 (2H, d, J=8.8Hz), 8.07 (4H, ABq, J=10.8Hz), 8.09-8.13 (1H, m), 8.79 (1H, d, J=7.9Hz), 8.55-9.00 (1H, br s)

MASS (m/z) : 1311.3 ($M-H^+$)

Elemental Analysis Calcd. for $C_{59}H_{80}N_{10}O_{20}S_2 \cdot 10H_2O$:
C 47.45, H 6.75, N 9.38

Found : C 47.68, H 6.27, N 9.21

Example 4

IR (KBr) : 1648.8, 1631.5, 1540.8, 1513.8, 1452.1 cm^{-1}

NMR (DMSO-d_6, δ) : 0.95 (3H, d, J=6.6Hz), 1.07 (3H, d, J=6Hz), 1.1-2.7 (21H, m), 2.7-5.5 (32H, m), 6.68-6.74 (2H, m), 6.9-6.94 (1H, m), 7.13 (2H, d,

J=5.7Hz), 1.05-1.04 (5H, m), 1.50-5.30 (52H, complex m), 6.67 (1H, d, J=5.7Hz), 6.73-6.80 (1H, m), 7.01 (1H, d, J=1.6Hz), 7.08 (2H, d, J=9Hz), 7.4-7.8 (3H, m), 7.85 (2H, d, J=8.7Hz), 8.07 (4H, ABq, J=9Hz), 8.31 (1H, d, J=6.9Hz), 8.71 (1H, s), 8.91 (1H, d, J=7.4Hz)

MASS (m/z) : 1319.4 ($M-H^+$)

Elemental Analysis Calcd. for $C_{60}H_{80}N_{12}O_{18}S_2 \cdot 9H_2O$:
C 48.57, H 6.66, N 11.33

Found : C 48.77, H 6.54, N 11.25

Example 8

IR (KBr) : 1635.3, 1529.3, 1519.6, 1467.6, 1446.4, 1257.4 cm^{-1}

NMR (DMSO-d_6, δ) : 0.91 (3H, t, J=7Hz), 0.96 (3H, d, J=8.3Hz), 1.12 (3H, d, J=5.6Hz), 1.2-2.6 (17H, m), 2.6-5.4 (29H, m), 6.71 (1H, d, J=8Hz), 6.77 (1H, br d, J=8Hz), 6.98 (1H, d, J=1.7Hz), 7.14 (2H, d, J=8.9Hz), 7.45 (1H, d, J=8.5Hz), 7.4-7.8 (3H, m), 7.90 (2H, d, J=8.8Hz), 8.05 (4H, s), 8.1-8.3 (1H, s), 8.64 (1H, d, J=6.9Hz), 8.85 (1H, s)

MASS (m/z) : 1278.3 ($M-H^+$)

Elemental Analysis Calcd. for $C_{57}H_{73}N_{11}O_{19}S_2 \cdot 9H_2O$:
C 47.46, H 6.36, N 10.68

Found : C 47.58, H 6.17, N 10.62

Example 9

IR (KBr) : 3361.3, 2937.1, 1635.3, 1523.5, 1461.8, 1251.6 cm^{-1}

NMR (DMSO-d_6, δ) : 0.97 (3H, d, J=6.8Hz), 1.10 (3H, d, J=5.9Hz), 1.2-5.3 (49H, m), 6.67-6.80 (2H, m), 7.01 (1H, d, J=1.6Hz), 7.15 (2H, d, J=9Hz), 7.4-7.8 (3H, m), 7.88 (2H, d, J=8.8Hz), 7.96 (4H, s), 8.35 (1H, d, J=8.3Hz), 8.7-8.8 (2H, m), 8.86 (1H, s)

API-ES MASS (Negative) : 1290.3 ($M-H^+$)

Elemental Analysis Calcd. for $C_{60}H_{86}N_{10}O_{20}S \cdot 7H_2O$:
C 50.55, H 7.07, N 9.83
Found : C 50.68, H 7.08, N 9.82

Example 13

IR (KBr) : 1648.8, 1631.5, 1540.8, 1511.9, 1454.1, 1238.1 cm^{-1}

NMR (DMSO-d_6, δ) : 0.8-1.3 (18H, m), 1.5-2.5 (24H, m), 2.61 (4H, br s), 2.8-5.4 (27H, m), 6.70 (1H, d, J=8.1Hz), 6.77 (1H, br d, J=10Hz), 6.92 (2H, d, J=9Hz), 7.00 (1H, d, J=1.6Hz), 7.42 (1H, d, J=8.6Hz), 7.5-7.7 (2H, m), 7.76 (2H, d, J=8.6Hz), 8.30 (1H, d, J=7.1Hz), 8.44 (1H, d, J=6.9Hz), 8.46-9.00 (1H, br s)

MASS (m/z) : 1241.3($M-H^+$)

Elemental Analysis Calcd. for $C_{58}H_{86}N_{10}O_{18}S \cdot 10H_2O$:
C 48.94, H 7.50, N 9.84
Found : C 49.19, H 7.33, N 9.73

Example 14

A solution of Starting compound (150 mg) in N,N-dimethylformamide (1.5 ml) was treated with diisopropylethylamine (166.5 mg) and ethyl formimidate hydrochloride (64.8 mg) and stirred 2 days at room temperature. Additional ethyl formimidate hydrochloride (39 mg) was added and stirring continued a further 3 hours 15 minutes. The reaction mixture was diluted with water and prified by ODS column chromatography, eluting with aqueous acetonitrile. Product-containing fractions were pooled, evaporated, and lyophilized to give Object compound as an amorphous white powder.

IR (KBr) : 1658.5, 1635.3, 1444.4, 1257.4 cm^{-1}

NMR (DMSO-d_6, δ) : 0.97 (3H, d, J=6.7Hz), 1.10 (3H, d, J=6.1Hz), 1.20-1.60 (8H, m), 1.60-2.50 (15H, m), 3.21 (3H, s), 2.80-5.30 (27H, m), 6.71 (1H, d,

8.2 (6H, m), 8.28 (1H, d, J=7Hz), 8.91 (1H, d, J=7.6Hz), 8.5-9.05 (1H, br s)

MASS (m/z) : 1331.2 ($M-H^+$)

Elemental Analysis Calcd. for $C_{61}H_{76}N_{10}O_{20}S_2 \cdot 10H_2O$:
C 48.41, H 6.39, N 9.25

Found : C 48.63, H 6.13, N 9.13

Example 17

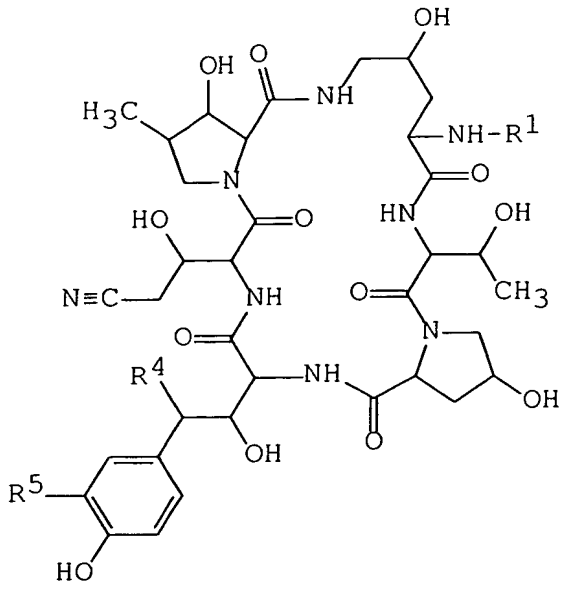
IR (KBr) : 1631.5, 1537.0, 1510.0, 1448.3, 1234.2 cm^{-1}

NMR (DMSO-d_6+D_2O, δ) : 0.96 (3H, d, J=6.7Hz), 1.05-1.15 (3H, m), 1.2-3.0 (33H, m), 3.15 (3H, s), 3.29 (2H, t, J=6.4Hz), 3.88 (2H, t, J=6.4Hz), 3.6-4.5 (14H, m), 4.7-4.85 (2H, m), 6.73-7.04 (9H, m), 7.75-7.9 (2H, m)

MASS (m/z) : 1311.4 ($M-H^+$)

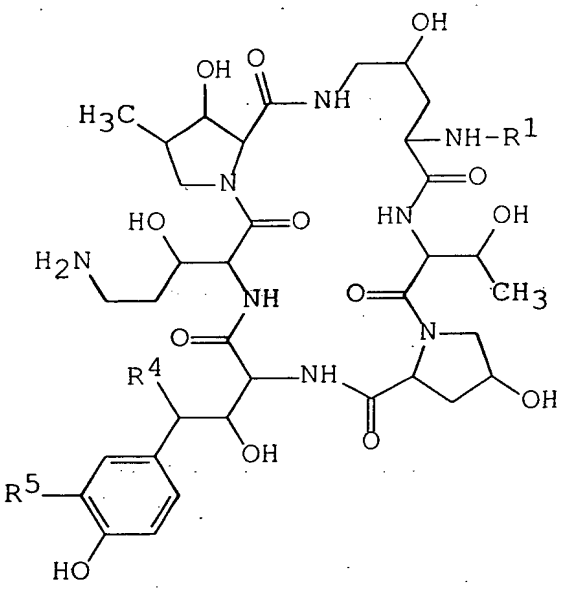
Elemental Analysis Calcd. for $C_{61}H_{88}N_{10}O_{20}S \cdot 10H_2O$:
C 49.05, H 7.29, N 9.38

Found : C 48.78, H 6.83, N 9.27



(II)

wherein R^1, R^4 and R^5 are as defined in claim 1, or a salt thereof, to give a compound (Ia) of the formula :



(Ia)

wherein R^1, R^4 and R^5 are as defined in claim 1, or a salt thereof, or

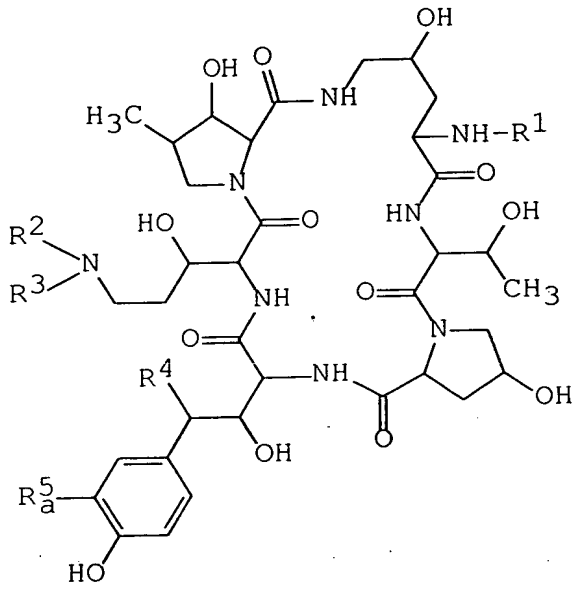
wherein R^1, R^4 and R^5 are defined in claim 1,

R^2_a is hydrogen, lower alkyl which may have one or more suitable substituent(s) or, acyl group, and

R^3_a is lower alkyl which may have one or more suitable substituent(s), or acyl group,

or a salt thereof, or

iii) reducing a compound (Ic) of the formula :



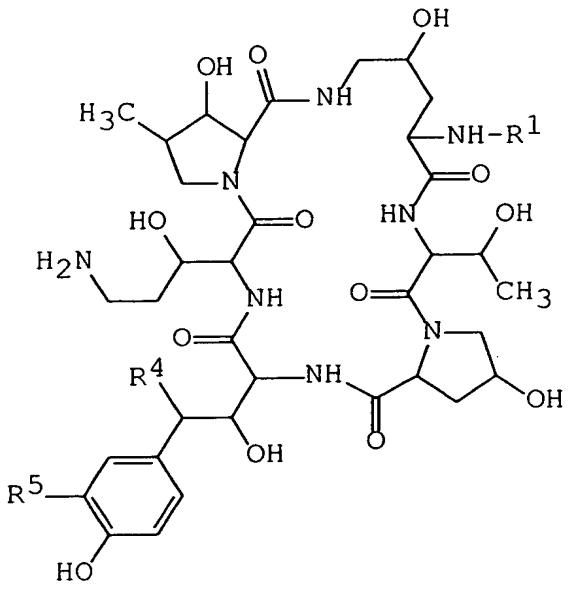
(Ic)

wherein R^1, R^2, R^3 and R^4 are defined in claim 1, and

R^5_a is hydroxysulfonyloxy,

or a its reactive derivative at the sulfonic acid group, or a salt thereof, to hydrolysis reaction of the sulfonic acid group, to give a compound (Id) of the formula :

protective group, to give a compound (Ia) of the formula :



(Ia)

wherein R^1, R^4 and R^5 are defined in claim 1, or a salt thereof.

3. A pharmaceutical composition which comprises, as an active ingredient, a compound of Claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carrier or excipients.

4. Use of a compound of Claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament.

5. A compound of Claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

6. A method for the prophylactic and/or therapeutic treatment of infectious diseases caused by pathogenic microorganisms, which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.

DOCKET NO.: 215095US0PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: TOJO Takashi et al.
SERIAL NO.: NEW U.S. PCT APPLICATION
FILED: HEREWITH
INTERNATIONAL APPLICATION NO.: PCT/JP00/02710
INTERNATIONAL FILING DATE: April 25, 2000
FOR: NEW COMPOUND

REQUEST FOR PRIORITY UNDER 35 U.S.C. 119 AND THE INTERNATIONAL CONVENTION

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In the matter of the above-identified application for patent, notice is hereby given that the applicant claims as priority:

COUNTRY	APPLICATION NO	DAY/MONTH/YEAR
Australia	PP 9997	27 April 1999

Certified copies of the corresponding Convention application(s) were submitted to the International Bureau in PCT Application No. PCT/JP00/02710. Receipt of the certified copy(s) by the International Bureau in a timely manner under PCT Rule 17.1(a) has been acknowledged as evidenced by the attached PCT/IB/304.

Respectfully submitted,
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REQUEST FOR CONSIDERATION OF DOCUMENTS CITED IN INTERNATIONAL SEARCH REPORT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In the matter of the above-identified application for patent, notice is hereby given that applicant(s) request that the Examiner consider the documents cited in the International Search Report according to MPEP §609 and so indicate by a statement in the first Office Action that the information has been considered. When the Form PCT/DO/EO/903 indicates both the search report and copies of the documents are present in the national stage file, there is no requirement for the applicant(s) to submit them (1156 O.G. 91 November 23, 1993).

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

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